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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

VICKI COLLINS
(Type or print name of person mailing paper)

Date: September 16, 1998

Vicki Collins
(Signature of person mailing paper)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of	)	Group Art Unit: 1614
Munger et al	)	Docket No. 230
Serial No: 08/900,752	)	Examiner: J. Reamer
Filed: July 25, 1997	)	
Title: NUCLEOTIDE ANALOG COMPOSITION AND SYNTHESIS METHOD	)	

RESPONSE UNDER 37 C.F.R. 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicants submit this paper in response to the Office action mailed on April 16, 1998, with time for response set to expire on July 16, 1998. Provision for extension of time to September 16, 1998 accompanies this paper.

Remarks

The Office returned initialed two 1449 forms with the Office action. Applicants mailed two additional IDS submissions on February 2, 1998, and March 4, 1998. Applicants would appreciate the Office returning the initialed 1449 forms from these later submissions with the next communication to Applicants. In the event that the Office did not receive these submissions, Applicants attach a copy of the 1449 form and the date stamped post card that

the PTO returned with each submission. The undersigned requests the Examiner to call him if the Office did not receive the cited references.

Related pending application

Applicants note that related subject matter is pending in application serial No. 08/900,746 (" '746"), which was filed on July 25, 1997 and has a priority date of July 26, 1996. The '746 application discloses and claims salts of bis(POC) PMPA. At page 37, lines 16-19 it contains the following disclosure: "Suitable salts for purification include the sulfuric acid, phosphoric acid, lactic acid, or citric acid salts of the diester or monoester compounds of structures (1) or (1a)." Compounds (1) and (1a) include bis(POC) PMPA.

The rejection under 35 U.S.C. § 103(a)

The Office rejected claims 1-20 as unpatentable over Sueoka et al. or Starrett et al. in combination with Berge et al. (*J. Pharm. Sciences* 66:1-19, 1977, of record). Applicants respectfully traverse the rejection.

Unexpected properties. Applicants direct the Office's attention to example 3 at pages 27-28. The data at page 28 shows that the fumarate salt of bis(POC) PMPA was unexpectedly more stable to storage at elevated relative humidity and temperature than the citrate salt. For example, after 60 days at 40° C and 75% relative humidity, 2.9% of the fumarate salt of bis(POC) PMPA converted to mono(POC) PMPA, while 22.4% of the citrate salt converted to mono(POC) PMPA. The cited art shows that one could not have predicted this improvement. Berge, a review article that discusses pharmaceutical salts, states at page 1, column 2:

> "Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles."

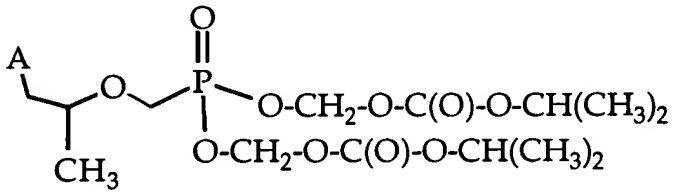
At page 2, column 1, Berge states that a large number of salts exist and that chemists synthesize many new ones each year. Applicants respectfully submit that the fumarate salt of bis(POC) PMPA is patentable based on its unexpected stability properties compared to the salt made from the structurally similar citric acid. Applicants note that Berge lists citric acid as a possible salt compound.

Prima facie obviousness. To maintain a rejection under Section 103 the Office must maintain a *prima facie* case of obviousness. *In re Fine,* 837 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Establishing or maintaining prima facie obviousness requires the Office to show some objective teaching in the cited references that would lead an individual to combine the relevant teachings as evidence of obviousness. *In re Lalu,* 223 U.S.P.Q. 1257 (Fed. Cir. 1987). One must find both the suggestion and the expectation of success in the cited art, not in the applicant's disclosure. *In re Dow Chemical Co.* 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). One can not use hindsight reconstruction using applicant's disclosure and claims as a guide to pick and choose among isolated elements to arrive at the claimed invention. *In re Fine, supra.*

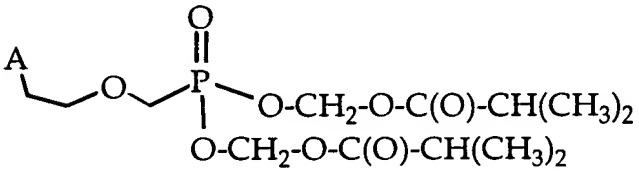
The Office made of record two references each by Sueoka et al. and Starrett et al. However, the Office did not specify which cited Sueoka et al. or Starrett et al. reference formed the basis for the rejection. Sueoka et al., Pharmacokinetics of Alkoxycarbonyloxy Ester Prodrugs of PMPA in Dogs, AAPS, Western Regional Meeting, April 24-25, 1997 (abstract) and Sueoka et al., Pharmacokinetics of Alkoxycarbonyloxy Ester Prodrugs of PMPA in Dogs, AAPS, Western Regional Meeting, April 24-25, 1997 (poster) (both of record) both disclose solutions containing 9-[2-(*R*)-[[bis[[(isopropoxy-carbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]adenine ("bis(POC) PMPA"). Both Sueoka references state that bis(POC) PMPA and a related prodrug had the highest oral bioavailabilities, about 30%, of the compounds tested. Neither Sueoka reference suggests a reason that would lead one to try to enhance any particular property of bis(POC) PMPA.

The Office made of record Starrett et al.,*J. Med. Chem.* 37:1857-1864, 1994 and Starrett et al., *Antiviral Res.* 19:267-273, 1992. The Office did not specify which cited Starrett et al. reference formed the basis for the rejection.

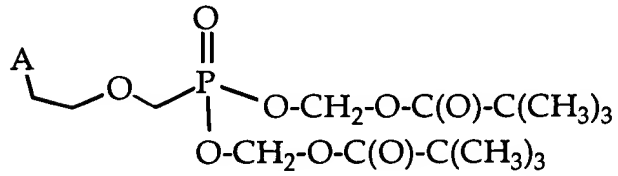
Neither Starrett reference of record disclosed bis(POC) PMPA. Instead, they disclosed (acyloxy)alkyl prodrugs of PMEA, a nucleotide analog that is structurally related to PMPA. The structures below show the closest structure in the Starrett papers (*J. Med. Chem.* 1994, compound **10b** at page 1858, scheme 2; *Antiviral Res.* compound **2** at page 269, figure 1) compared to the parent compound of claim 1.



Claim 1



Starrett, *J. Med. Chem.* 1994



Starrett, *Antiviral Res.* 1992

The comparison above shows, among other structural differences, the claim 1 compound is a carbonate, -O-C(O)-O-R, while Starrett's compound **10b** and **2** are (acyloxy)alkyl compounds, -O-C(O)-R. They lack the oxygen atom linked to the terminal -$CH(CH_3)_2$ group in the claim 1 compound. The cited references do not constitute *prima facie* obviousness, because they do not disclose any compound that renders bis(POC) PMPA obvious.

Starrett (*Antiviral Res.* 19:267-273, 1992) disclosed silver and other salts of PMEA at pages 268 -269. Starrett examined these salts as intermediates to make piv_2PMEA. This reference did not disclose any salt of piv_2PMEA.

Applicants respectfully submit that the Office has not established a *prima face* case of obviousness since the references do not contain any objective teaching that would lead one to combine them. *In re Lalu, supra.* The Sueoka references both stated that bis(POC) PMPA had high

bioavailability. Neither Sueoka reference mentioned any property of bis(POC) PMPA that one would want to improve by forming a salt. The Sueoka poster concludes by stating that due to the favorable bioavailability and intestinal stability properties of bis(POC) PMPA, it was selected for clinical evaluation. Berge makes it clear that the artisan could not have predictably selected a salt that would confer desired characteristics on the parent compound.

The cited references do not identify which property of bis(POC) PMPA one would want to improve. Nor do they provide a reasonable basis for an expectation of success. Thus, Sueoka and Starrett combined with Berge do not suggest that one would want to prepare any bis(POC) PMPA salt, much less the fumarate salt. Even if the skilled artisan were to arbitrarily select a certain property to improve, Berge makes it clear that one could not predict success. As noted above, the suggestion and the expectation of success must come from the cited art and not the applicant's disclosure. *In re Dow Chemical Co., supra*. One can only arrive at applicants invention using hindsight reconstruction, which is impermissible. *In re Fine, supra*. Applicants respectfully request the Office to reconsider and withdraw the rejection. Applicants respectfully request the Office to reconsider and withdraw the rejection.

Conclusion

Applicants believe the application is in condition for allowance and they respectfully solicit an early notice to that effect.

Respectfully submitted,

Daryl D Muenchau

Dated: 9-11-98

Daryl D. Muenchau, Reg. No. 36,616
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
phone: 650-573-4712
FAX: 650-573-4899

Attachments:
1. Postcard and 1449 form accompanying the IDS mailed on February 2, 1998
2. Postcard and 1449 form accompanying the IDS mailed on March 4, 1998